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Gynecologic Oncology

Systemic Treatment of Metastatic/Recurrent Uterine Leiomyosarcoma: A Changing Paradigm

Rebecca C. Arend,[a] Michael D. Toboni,[a] Allison M. Montgomery,[a] Robert A. Burger,[b] Alexander B. Olawaiye,[c] Bradley J. Monk,[d] Thomas J. Herzog[e]

[a]Department of Obstetrics and Gynecology, University of Alabama School of Medicine, Birmingham, Alabama, USA; [b]Department of Obstetrics and Gynecology, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA; [c]Department of Obstetrics, Gynecology, and Reproductive Sciences, Magee-Womens Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [d]Arizona Oncology (US Oncology Network), University of Arizona and Creighton University, Phoenix, Arizona, USA; [e]Department of Obstetrics and Gynecology, University of Cincinnati Cancer Institute and College of Medicine, Cincinnati, Ohio, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Uterine cancer • Leiomyosarcoma • Soft tissue sarcoma • Uterine sarcoma • L-sarcoma chemotherapy

Abstract

The treatment of metastatic and recurrent uterine leoimyosarcoma (uLMS) has evolved rapidly in the past several years. Leoimyosarcoma is extremely aggressive and responds poorly to traditional chemotherapeutics. Recent regulatory approval of novel treatment options has significantly expanded the therapeutic armamentarium, and the addition of these therapies has challenged clinicians to select and optimally sequence these new compounds. Additionally, the potential role of immunotherapy is being assessed in current uLMS clinical trials. Given the increasing number of agents available both in the U.S. and globally, a treatment template that addresses optimal sequencing based upon expert consensus would be useful. Current guidelines, although listing various options, lack granularity by line of therapy. Most patients with leiomyosarcoma, even in early stage, are treated with surgery followed by adjuvant chemotherapy despite uLMS being relatively chemoresistant. Adjuvant chemotherapy often includes the combination of gemcitabine and docetaxel with or without doxorubicin in first-line systemic therapy, but these cytotoxic agents only provide patients with advanced disease a 5-year survival <30%. This review will focus on examination of current guidelines and consensus building for optimal sequencing of systemic therapies for advanced or recurrent uLMS. Critical ongoing studies investigating novel approaches including immunotherapeutics and genetic alterations also will be discussed. ***The Oncologist*** 2018;23:1533–1545

Implications for Practice: Recent regulatory approval of novel treatment options has significantly expanded the therapeutic armamentarium, and the addition of these therapies has challenged clinicians to select and optimally sequence these compounds. This review will focus on examination of current guidelines and consensus building for optimal sequencing of systemic therapies for advanced or recurrent uterine leoimyosarcoma.

Introduction

Approximately 5,058 cases of uterine sarcomas are expected to be diagnosed in the U.S. in 2018 with a mortality rate as high as 29% [1, 2]. For leiomyosarcoma (LMS), high recurrence rates are observed in all stages despite surgery and adjuvant treatment [3]. The 5-year survival rate for stage I disease is 76%, whereas stages II–IV are associated with 60%, 45%, and 29% survival, respectively [4]. Most patients will not live more than 12 months after recurrence [5, 6]. In advanced-stage patients (stage III/IV), current guidelines support the role of chemotherapy in patients following definitive surgery (adjuvant) and in patients who have unresectable disease. However, the optimal regimen, order, and dose of systemic chemotherapy remains unclear. Here, we review the rationale behind the regimens and types of chemotherapy that are being used for metastatic and recurrent uterine LMS (uLMS).

Background

Uterine sarcomas are a heterogeneous group of tumors, including carcinosarcomas, leiomyosarcomas, endometrial

Correspondence: Thomas J. Herzog, M.D., Department of Obstetrics and Gynecology, University of Cincinnati Cancer Institute and College of Medicine, 231 Albert Sabin Way, Suite 2005H, ML0662, Cincinnati, Ohio 45267-0662, USA. Telelphone: 513-584-6373; email: thomas.herzog@uc.edu Received February 18, 2018; accepted for publication June 5, 2018; published Online First on August 23, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0095

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Table 1. Types of uterine sarcomas

Type of uterine sarcoma	Immunohistologic markers
Leiomyosarcoma	Ki67, p53, p16, SMA, and h-caldesmon [63]
Endometrial stromal sarcoma	CD10 [64]
High-grade undifferentiated sarcoma	Ki67, p53, and p16 [63]
Adenosarcoma with sarcomatous overgrowth	CD10, +/− ER and PR [65]
Carcinosarcoma (MMMT)	p53, WT1, SMA, desmin, myogenin, and bcl-2 [66]

Abbreviation: ER, estrogen receptor; MMMT, malignant mixed Müllerian tumor; PR, progesterone receptor; SMA, smooth muscle actin.

Table 2. International Federation of Gynecology and Obstetrics staging

I. Tumor limited to the uterus
A. Tumor ≤5 cm in greatest dimension
B. Tumor >5 cm
II. Tumor extends beyond the uterus, within the pelvis
A. Tumor involves adnexa
B. Tumor involves other pelvic tissues
III. Tumor infiltrates abdominal tissues (not just protruding into the abdomen)
A. One site
B. More than one site
IV. Tumor is invasive or metastatic
A. Tumor invades bladder or rectum
B. Distant metastasis (excluding adnexa, pelvic, and abdominal tissue)

stromal sarcomas, adenosarcomas with sarcomatous overgrowth, and high-grade undifferentiated sarcomas (Table 1) [7]. The natural history, prognosis, and treatment of uterine sarcomas vary by histology and grade. There are limited data regarding the rarest subtypes. When carcinosarcoma is excluded, LMS is the most common type of uterine sarcoma [8, 9]. uLMS is composed of malignant smooth muscle with significant cellularity, nuclear atypia, necrosis, high mitotic rate, invasion, and metastases. LMS is diagnosed based on the Stanford criteria, requiring the presence of at least two of the following characteristics: (a) high mitotic rate >10 figures per 10 high-power fields, (b) moderate to severe cellular atypia, and (c) areas of coagulative tumor cell necrosis [10]. Leiomyosarcomas typically express smooth muscle markers, including smooth muscle actin and h-caldesmon. There has been significant variation in the literature as to the percentage of estrogen and/or progesterone receptor positivity, varying from 7% to 71% [11]. uLMS harbors multiple complex chromosomal abnormalities with no single specific translocation. Abnormalities of the *p53*, *MDM2*, and *DCC* genes have been described [12]. Given the complexity of the histology of uLMS, it is important that all cases are reviewed by a gynecological pathologist with expertise in this area.

Median age at diagnosis is 56 years. Most experts believe uLMS arises de novo and only rarely transitions from benign leiomyoma, occuring approximately 5%–10% of the time. The incidence of occult LMS is between 0.2% and 0.7% [13]. It typically presents with abnormal bleeding like most uterine cancers; however, it has been linked to some unusual presentations, including the Leser-Trélat sign, which is the rapid onset of seberroheic keratoses that can be a sign of underlying malignancy [14].

Prior to 2009, all uterine sarcomas were staged according to the criteria for uterine carcinomas. In 2009, the International Federation of Gynecology and Obstetrics created a distinct surgical staging system for uterine sarcomas excluding uterine carcinosarcoma (Table 2).

The initial treatment of LMS involves removal via hysterectomy; however, bilateral salpingo-oophorectomy remains controversial. These tumors may express estrogen receptors, and thus eliminating estradiol production may limit recurrence. However, this remains hypothetical as retrospective data analysis has revealed no outcome differences between hysterectomy with bilateral salpingo-oophorectomy versus hysterectomy alone and must be weighed against the advantages of ovarian preservation [4, 15]. A review of cases by Pritts et al. did not conclusively reveal any outcome differences related to morcellation verses en bloc removal [16]. However, an expert opinion by Chalas, as well as a consensus review by Hensley et al., states that morcellation should be avoided in any suspected or diagnosed malignancy, including LMS [15, 17].

In stage I uLMS, Littell et al. found that observation with imaging after hysterectomy was equivalent to administration of adjuvant gemcitabine and docetaxel, which has been recommended for ongoing management in these women [18, 19]. The rate of lymphatic involvement is relatively low, ranging between 3.5% and 11% [3]. Therefore, if final pathology for presumed benign leiomyoma returns as LMS, it is not generally recommended to perform a second procedure to procure lymph nodes. In addition, administration of adjuvant gemcitabine and docetaxel is equivalent to observation in these patients. So, for stage I uLMS it is reasonable to defer therapy to use if a patient recurs. The most common metastatic sites are lung, liver, and bone. Even if the cancer has not metastasized, the risk of recurrence within 2–5 years is 40%–70% [3]. Once metastatic disease is diagnosed, either initially or at recurrence, median survival is 1 year [5, 6]. Given the devastating nature of this disease, establishing a treatment consensus for advanced and recurrent uLMS is vitally important.

Single Agents in Metastatic uLMS

Doxorubicin (adriamycin) is an active single agent for uLMS and is less toxic than combination regimens. Three GOG trials (GOG 20, 21, 42) conducted in the 1980s assessed single-agent adriamycin for the treatment of uLMS. In GOG 20, 56% of patients did not recur, but there was no survival difference observed for adjuvant doxorubicin versus observation, with or without radiation [20]. GOG 21 and 42 compared single-agent doxorubicin

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to doxorubicin with dimethyl tiazenoimidazole carboxamide (GOG 21) or cyclophosphamide (GOG 42), which showed no outcome difference for single-agent versus combination treatments [21, 22]. Judson et al. compared the efficacy of doxorubicin to pegylated liposomal doxorubicin (Doxil; Janssen Pharmaceutica, Beerse, Belgium) in 94 patients (35% with LMS) with advanced soft-tissue sarcoma (STS), and demonstrated similar activity in both with an improved toxicity profile in Doxil patients [23]. Gynecologic oncologists favor a dose of 60 mg/m^2 of doxorubicin for systemic treatment of LMS. However, medical oncologists recommend that the threshold dose for optimal activity appears be ≥60 mg/m^2 per 3-week cycle for metastatic STS, with most settling on a standard dose of 75 mg/m^2 per cycle [24]. This is an important distinction because there is not a consensus in regard to dosages between the two specialties. Cisplatin, ifosfamide, etoposide, paclitaxel, topotecan, trimetrexate, doxorubicin, temozolomide, and trabectedin have all shown modest to minimal response rates in advanced LMS in the upfront setting: 3%, 17%, 0%, 12%, 11%, 4%, 16%, 8%, and 9.5%, respectively (Table 3).

Other therapies included in the National Comprehensive Cancer Network (NCCN) list of recommended single agents include the following: (category 2A: dacarbazine, epirubicin, gemcitabine, pazopanib, temoxolomide), (category 2B: vinorelbine, eribulin), and (category 3: docetaxel; Table 3). Gemcitabine as a single agent has had response rates as high as 21% when a 1,000 mg/m^2 dose was administered over 30 minutes on days 1, 8, and 15, with cycles repeated every 28 days. Eribulin, an antimicrotular antineoplastic agent, is listed in the NCCN guidelines as an option for treatment of uterine sarcomas; however, it is not U.S. Food and Drug Administration (FDA) approved for this indication. It had equal efficacy when compared with dacarbazine, an alkylating antineoplastic agent, in a phase III trial that included patients with both LMS and liposarcoma (LPS). The median overall survival (OS) was 13.5 versus 11.5 months (hazard ratio [HR] 0.79), although the study was not powered for OS. When a subgroup analysis was performed in just the uLMS patients, there was no difference in OS (12.7 vs. 13) with an HR of 0.93 [25]. Although eribulin is not approved for uLMS in the U.S., it is approved for use in advanced LPS in the U.S., and for LMS and LPS in other countries.

Trabectedin interacts with DNA repair mechanisms as a minor groove binder and major groove binder. It modulates transcriptional regulation by displacing transcription factor and fusion proteins, specifically the *FUS-CHOP* fusion gene, the hallmark of myxoid liposarcoma. Additionally, it inhibits transcription by blocking RNA polymerase II and affects the tumor microenvironment by inhibiting CCL2, a proinflammatory mediator [26]. Trabectedin (ET-743) gained approval in Europe in 2007, and in 2015 it was approved in the U.S. for use in advanced LMS and LPS after failure of anthracycline therapy [27, 28]. The dose and schedule was determined by a phase II randomized trial of two different schedules in advanced or metastatic LPS or LMS after failure of prior anthracyclines and ifosfamide, which included 260 patients (177 LMS patients). The median time to progression favored the every-3-week 24-hour schedule. Its FDA approval was based on SAR 3007, which was a phase III randomized trial comparing trabectedin with dacarbazine in metastatic LPS or LMS after an anthracycline- and ifosphamide-containing regimen or an anthracycline-containing regimen and one additional chemotherapy regimen. The median progression-free survival (PFS) favored trabectedin over dacarbazine: 4.2 versus 1.5 months (HR 0.55; $p < .001$) [29, 30]. In patients with uLMS specifically, trabectedin significantly improved PFS compared with treatment with dacarbazine (median PFS: 4.01 months vs. 1.54 months [HR 0.57; $p = .0012$]; Fig. 1) [31]. Clinical trials with trabectedin are listed separately in Table 3.

Targeted Therapy

The oral multikinase angiogenesis inhibitor, pazopanib, is FDA approved for advanced STS other than LPS or gastrointestinal stromal tumors that fail anthracycline therapy. It was initially explored in advanced STS in the EORTC Study 62043, which was a phase II study that included 41 patients with LMS. The 12-week progression-free rate (primary endpoint) was 44% in this population [32]. It was later studied in a multicenter, international, double-blind, placebo-controlled phase III PALETTE study (EORTC study 62072) in STS patients, including 165 LMS patients, who had received at least two lines of prior chemotherapy. This trial showed a 6% response rate (RR) with a 4.6-month PFS and a 12.5-month OS, compared with the 1.6-month PFS (HR 0.31) and 10.7-month OS (HR 0.86) in the placebo arm [33]. The LMS cohort specifically had a PFS of 4.6 months versus 1.9 months (HR 0.37).

Additionally, Benson et al. published a retrospective analysis of 44 patients with uterine sarcoma treated with pazopanib; 39 patients had uLMS. Despite over 85% receiving prior treatment in the uterine sarcoma group, pazopanib showed signs of activity with similar outcomes to patients with nonuterine STS. Median PFS was 3.0 months (95% confidence interval [CI] 2.5–4.7) in uterine versus 4.5 (95% CI 3.7–5.1) in nonuterine STS. Median OS was 17.5 months (95% CI 11.1–19.6), which was longer than the nonuterine population OS of 11.1 months (95% CI 10.2–12.0; $p = .352$) [34].

Sorafenib and sunitinib, tyrosine kinase inhitors, showed minimal response rates in advanced and/or recurrent LMS (2.7% and 8.7%, respectively) and thus are not included in the NCCN recommended guidelines (Table 3) [35].

Combination Agents in Metastatic uLMS

Combination chemotherapy yields better response rates than single agents in patients who can tolerate more aggressive regimens. Given that doxorubicin and ifosfamide are the most active single agents in STS, the combination of the two was evaluated by the GOG in a phase II study and showed a response rate of 29%; however, this

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Table 3. Chemotherapy agents and trials

Drug (NCCN endorsement)	Patients	Number of arms	Response rate	PFS, months	OS, months	Author and GOG protocol	Year
I. First-line chemotherapy, single-agent/single-arm studies							
Cisplatin	*n* = 96, *n* = 33 (uLMS), advanced or recurrent uterine sarcomas	Single arm	19% (all), 3% (uLMS)	3.4	23.2	Thigpen [67]	1991
Ifosfamide[a]	*n* = 35, uLMS	Single arm	17%	—	—	GOG-26C Sutton [68]	1992
Etoposide	*n* = 28, advanced, persistent, or recurrent uLMS	Single arm	0%	2.1	9.2	GOG-87B Thigpen [69]	1996
Epirubicin[a]	*n* = 20, uterine sarcoma	Single arm	20% CR	—	48 (responders), 6 (nonresponders)	GOG-87D Lissoni [70]	1997
Paclitaxel	*n* = 33, All uLMS	Single arm	12%	N/A	N/A	Sutton [71]	1999
Topotecan	*n* = 29, advanced, persistent, or recurrent uLMS	Single arm	11%	N/A	N/A	GOG-87G Miller [72]	2000
Trimetrexate	*n* = 23, uLMS only	Single arm	4%	2.2	7.2	GOG-87H Smith [73]	2002
Lipsomal Doxorubicin (Doxil)[a]	*n* = 31, advanced or metastatic uLMS	Single arm	16.1%	4.1	N/A	GOG-131D Sutton [74]	2005
Trabectedin[a] (for uLMS treated with a prior anthracyline-containing regimen)	*n* = 20, advanced, persistent, or recurrent uLMS	Single arm	9.5%	5.8	26.1	GOG-87J Monk [75] GOG-87M	2012
II. First-line and recurrent chemotherapy with a single-agent arm							
Adriamycin[b] vs. Observation	*n* = 75 vs. *n* = 81 stage I/II uterine sarcomas	Two arms	59% vs. 47% without recurrence	N/A	73.7 vs. 55.0	Omura [76]	1985
Etoposide	*n* = 27 uLMS	Single arm	7.4%	2.1	7.6	GOG-20 Rose [77]	1998
Docetaxel[a] (category 3)	*n* = 37 resistant STS	Single arm	2.7% (1 partial remission)	42 days	350 days	GOG-131B Santoro [78]	1999
CAELYX (Doxil)[a] vs. Doxorubicin[b]	*n* = 50 (*n* = 18 uLMS) vs. *n* = 44 (*n* = 13 uLMS) advanced STS	Two arms	10% vs. 9%	—	—	Judson [79]	2001
Temozolomide[a]	*n* = 25 unresectable or metastatic STS	Single arm	8%	2.0	13.2	Talbot [80]	2003
Paclitaxel	*n* = 48 recurrent or advanced uLMS	Single arm	8.3%	1.5	12.1	Gallup [81]	2003
Gemcitabine[a]	*n* = 42 recurrent or persistent uLMS	Single arm	20.5%, 21% no radiation	4.9	—	GOG-131C Look [82]	2004
Vinorelbine[a] (category 2B)	*n* = 58 STS previously treated	Single arm (retrospective)	6%	1.8	6.4	GOG-131E Anderson [83]	2006
Gemcitabine & Docetaxel[b] vs. Gemcitabine[a] alone	*n* = 73 (*n* = 29 uLMS) vs. *n* = 49 (*n* = 9 uLMS) recurrent or progressive STS	Two arms	16% vs. 8%	6.2 vs. 3.0	17.9 vs. 11.5	Maki [84]	2007

Sorafenib	*n* = 122 (*n* = 37 uLMS) metastatic or recurrent sarcomas	Single arm	2.7%	3.2	22.4	Maki [85]	2009
Sunitinib	*n* = 23 persistent or recurrent uLMS	Single arm	8.7%	1.54	15.1	Hensley [86] GOG-231C	2009
Pazopanib[a] (recurrent or metastatic with progression on prior cytotoxic chemotherapy) vs. Placebo	*n* = 246 vs.. *n* = 123 metastatic STS (low-high grade)	Two arms	6% vs.. 0%	4.6 vs.. 1.6	12.5 vs.. 10.7	van der Graaf [87]	2012
Eribulin[a] (category 2B) vs. Dacarbazine[a]	*n* = 228 (*n* = 68 uLMS) vs. *n* = 224 (*n* = 63 uLMS) liposarcoma or LMS	Two arms	33% vs. 29%	2.6 vs. 2.6	13.5 vs. 11.5	Schoffski [88]	2016
III. First line, multiagent							
Doxorubicin & Ifosfamide[a]	*n* = 33 advanced or recurrent uLMS	Single arm	30.3%	N/A	9.6	Sutton [89]	1996
Gemcitabine & Docetaxel[b]	*n* = 39 stages I–IV high-grade uLMS	Single arm	35.8%	4.4	16.1	GOG-87F Hensley [90]	2008
Gemcitabine & Docetaxel[b]	*n* = 23 stage I–IV high-grade uLMS	Single arm	N/A	13	Not been reached	GOG-87L Hensley [91]	2009
Gemcitabine & Docetaxel[b] followed by Doxorubicin	*n* = 46 uterus-limited, high-grade uLMS (stages I–III)	Single arm	78% progression-free at 2 years, 57% at 3 years	Not been reached	Not been reached	Hensley [92]	2013
Gemcitabine, Docetaxel, & Bevacizumab vs. Gemcitabine, Docetaxel, & Placebo	*n* = 53 vs. *n* = 54 metastatic, unresectable uLMS	Two arms	35.8% vs. 31.5%	4.2 vs. 6.2	23.3 vs. 26.9	Hensley [93] GOG-250	2015
Trabectedin & Doxorubicin	*n* = 109 (*n* = 47 uLMS) metastatic or unresectable uLMS or soft tissue LMS	Single arm	59.6% (uLMS specific)	8.2	20.2	Pautier [94]	2015
IV. Mixed first and second line, multiagent							
Gemcitabine & Docetaxel[b]	*n* = 34 (*n* = 29 uLMS) unresectable disease	Single arm	26%	5.6	17.9	Hensley [95]	2002
Gemcitabine & Docetaxel[b]	*n* = 42 advanced uLMS	Single arm	35.8%	4.4	16.1	Hensley [90]	2008
Olaratumab & Doxorubicin[b] vs. Doxorubicin[b] alone	*n* = 66 (*n* = 24 uLMS) *n* = 67 (*n* = 27 uLMS) locally advanced or metastatic STS vs.	Two arms	18.2% vs. 11.9%	6.6 vs. 4.1	26.5 vs. 14.7	GOG-87L Tap [96]	2016
Gemcitabine & Vinorelbrine[a]	*n* = 40 unresectable or metastatic STS, *n* = 19 LMS	Single arm	2.5% CR, 10% PR	3.4	—	Dileo [97]	2007
V. Trabectedin trials							
Trabectedin every 3 weeks 24-hour vs. Trabectedin every week 3-hour Trabectedin	*n* = 136 (*n* = 32 (uterine) vs. *n* = 134 (*n* = 28 uterine) unresectable and/or metastatic relapse or progressive liposarcoma or LMS	Two arms	5.6% vs. 1.6%	3.3 vs. 2.3	13.9 vs. 11.8	Demetri [98]	2009

(continued)

Table 3. (continued)

Drug (NCCN endorsement)	Patients	Number of arms	Response rate	PFS, months	OS, months	Author and GOG protocol	Year
Trabectedin[a]	*n* = 20 advanced, persistent, or recurrent uLMS	Single arm	10%	5.8	>26.1 (median not reached)	Monk [75] GOG-87M	2012
Trabectedin	*n* = 807 advanced STS	Single arm	6.9%	—	11.9	Samuels [99]	2013
Trabectedin[a] vs. Dacarbazine[a]	*n* = 381 (*n* = 144 uLMS) vs. *n* = 190 (*n* = 88 uLMS) advanced LMS liposarcoma	Two arms	11% vs. 9%	4.0 vs. 1.5	13.4 vs. 12.9	Hensley [100]	2016
Trabectedin & Doxorubicin	*n* = 108 (*n* = 74 (uLMS) measurable metastatic or unresectable uLMS or soft-tissue LMS	Single arm	59.6% (uLMS specific)	8.2	20.2 (uLMS specific)	Pautier [94]	2015
Trabectedin & Doxorubicin vs. Doxorubicin[b] alone	*n* = 55 vs. *n* = 60 locally advanced nonresectable or metastatic STS	Two arms	17% vs. 17%	5.7 vs. 5.5	13.3 vs. 13.7	Martin-Broto [101]	2016

[a]Included in the NCCN Guidelines Version 1.2018 Uterine Sarcoma as other options (combination and single agent) [102].
[b]Included in the NCCN Guidelines Version 1.2018 Uterine Sarcoma as preferred therapies.
Abbreviations: —, no data; LMS, leiomyosarcoma; N/A, not applicable; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival; STS, soft-tissue sarcoma; uLMS, uterine leiomyosarcoma.

response rate was similar to that observed in STS with doxorubicin alone (~25% RR) [36].

In 2002, Hensley et al. published the first trial using gemcitabine and docetaxel, the most commonly used combination regimen for treatment of uLMS. It was a single-institution phase II trial in patients with unresectable LMS who had received 0–2 prior chemotherapy regimens both with and without prior radiation [37]. This trial evaluated two different treatment doses depending on if the patient received prior radiation (675 gem/75 docetaxel) or did not receive prior radiation (900 gem/100 docetaxel). The two agents were given every 3 weeks for six cycles. The overall response rate in this trial was 53% (3 with complete response [CR], 15 with partial response [PR]) with a median PFS of 5.6 months and a median OS of 17.9 months. This was the first trial to demonstrate that combination gemcitabine and docetaxel was a tolerable and active treatment for unresectable disease, both with and without prior treatment. In 2007, Maki et al. published a study that compared gemcitabine with combination gemcitabine + docetaxel. This trial was done in all STS tumors and showed a response rate of 8% versus 16%, PFS of 3 versus 6.2 months, and an OS of 11.5 versus 17.9 months, supporting the use of the combination of gemcitabine with docetaxel over gemcitabine alone [38]. Interestingly, although the PFS and OS was calculated for all STS tumors, the authors reported treatment outcomes for the LMS tumors only. In LMS patients, 1/9 (11%) responded to gemcitabine alone, whereas 15/29 (52%) responded to the combination.

GOG 87L investigated the same regimen as Hensely in 2002, but this phase II trial was limited to patients with advanced, unresectable disease who had received no prior chemotherapy. Fifty percent of all patients (19/38) received six or more cycles. The response rate was 36% (15/42; CR 2/39, 4.8%; PR 13/39, 31%); 26.2% had stable disease (11/32); and 62% had some clinical benefit. Sixty percent of patients at 12 weeks had not progressed, and 41% of patients had not progressed at 24 weeks. Those who had either a complete or partial response had a response duration of 6 months, and the PFS was 4.4 months (Table 3) [39]. The same fixed-dose rate gemcitabine plus docetaxel achieved a high response rate in advanced, recurrent uLMS as a second-line treatment in GOG 131G. This was a phase II trial that demonstrated 50% of patients had stable disease and 27% showed a response to treatment (CR 6.3%, PR 20.8%) [39]. Given the activity of this regimen in advanced disease, it was later studied in patients with stage I–IV uLMS that had been completely resected, showing a median PFS of 13 months [40].

In 2013, Hensley et al. published SARC 005, a phase II trial of four cycles of fixed-dose-rate gemcitabine plus docetaxel followed by four cycles of doxorubicin in patients with disease limited to the uterus after complete resection. The median time to recurrence was 27.4 months (range 3–40 months). Seventy-eight percent (95% CI 67%–91%) were progression-free at 2 years, and 57% (95% CI 44%–74%) were progression-free at 3 years [41]. Despite a reported improvement in response with addition of doxorubicin to gemcitabine and docetaxel, not all providers are using this regimen as their standard. Many providers at

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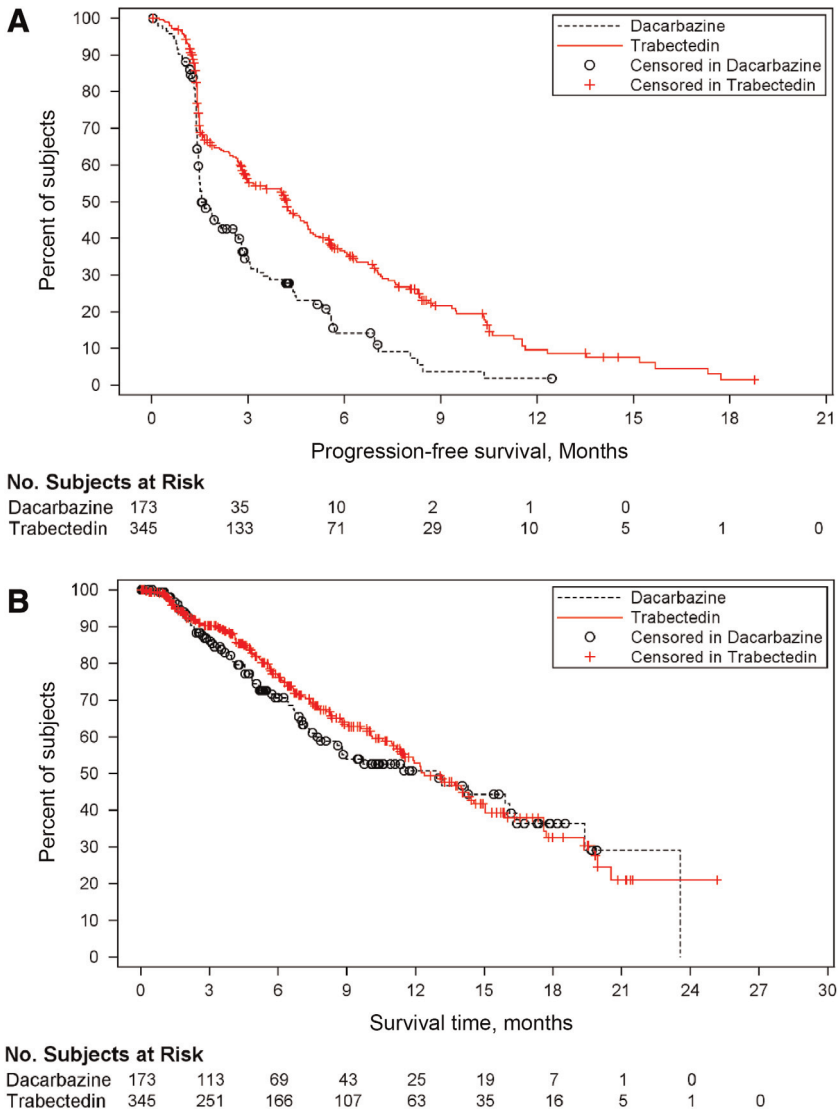

Figure 1. Kaplan-Meier curves of uLMS patients in Trabectedin vs. Dacarbazine trial. **(A):** Progression-free survival comparison. **(B):** Survival time comparison.

large academic centers continue to use gemcitabine and docetaxel without doxorubicin and later use doxorubicin when patients progress. Two years after SARC 005, Hensley et al. published GOG 250, which evaluated the role of bevacizumab in the management of metastatic LMS. The study was closed early for futility; there was no difference in PFS, OS, or objective response rates. The median PFS was 6.2 months in the control arm versus 4.2 months with bevacizumab (HR 1.12; p = .58). The mean duration of response was 8.6 months for gemcitabine and docetaxel plus placebo versus 8.8 months for gemcitabine and docetaxel plus bevacizumab. The response rate was 32% in the gemcitabine and docetaxel arm versus 36% in the gemcitabine and docetaxel plus bevacizumab arm [42].

Olaratumab, an anti-PDGFa monocolonal antibody, was FDA approved in 2016 for STS, but is not included in the most recent version of the Uterine 2017 NCCN guidelines. Approval was based on data comparing olaratumab with doxorubicin with doxorubicin alone in recent open-label phase Ib and phase II trials in advanced STS [43]. The median PFS was 6.6 versus 4.1 months (HR 0.672). The median OS was 26.5 versus 14.7 months (HR 0.46). The response rate was 18.8% with combination versus 12.3% with doxorubicin alone. The phase II trial was analyzed separately and showed a PFS of 8.2 versus 4.4 months and a response rate of 18% versus 8% with the same OS. The statistically significant difference in OS was consistent across stratifications, including LMS versus non-LMS subgroups [44].

The combination of trabectedin and doxorubicin was evaluated by the French Sarcoma Group as first-line treatment in advanced STS, and in uLMS patients the median PFS was 8.2 months [45]. The Spanish Group performed a phase II trial comparing the combination of trabectedin and doxorubicin with doxorubicin alone as first-line treatment for advanced STS, but the combination did not demonstrate superiority over doxorubicin alone [46].

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Table 4. Ongoing clinical trials

Drug(s)	Phase	Patient eligibility	Trial number
Trabectedin vs. best supportive care	III	STS (≤3 prior lines)	NCT02672527
Doxorubicin & trabectedin followed by trabectedin vs. doxorubicin	III	Metastatic or relapsed unresectable uLMS or soft-tissue LMS	NCT02997358
Gemcitabine & docetaxel ± olaratumab	Ib (open-label), II (randomized, double-blinded)	Advanced or metastatic disease (≤2 prior lines)	NCT02659020
Pembrolizumab	II	Unresectable, recurrent, and/or metastatic high grade STS or bone sarcoma (1–3 prior systemic therapies in metastatic setting)	NCT02301039
Olaratumab & doxorubicin	I	STS (including grade 1 liposarcoma with proven evolution to more aggressive disease)	NCT02783599
Clinical observation vs. docetaxel, doxorubicin hydrochloride, filgrastim, gemcitabine hydrochloride, & pegfilgrastim	III	uLMS, FIGO stage I (confined to corpus +/− cervix); required complete hysterectomy	NCT01533207
Letrozole vs. observation	II	uLMS limited to the uterus; must express ER positivity by IHC (>10%)	NCT00414076
Pembrolizumab	II	Grade 2 or 3 out of 3 UPS or dedifferentiated/pleomorphic LPS of the extremity (>5 cm)	NCT03092323
Pembrolizumab & doxorubicin	II	Unresectable or metastatic STS; has not received prior treatment with an anthracycline chemotherapy and/or anti-PD-1/PD-L1 therapy	NCT03056001
Axitinib & pembrolizumab	II	Sarcoma	NCT02636725
Pembrolizumab & gemcitabine	I, II	Undifferentiated pleomorphic sarcoma or LMS	NCT03123276
Doxorubicin hydrochloride & pembrolizumab	I, II	Metastatic or unresectable sarcoma	NCT02888665
Talimogene laherparepvec (T-VEC) & pembrolizumab	II	Metastatic and/or locally advanced sarcoma (at least 1 prior line of systemic therapy)	NCT03069378
MK3475 & metronomic cyclophosphamide	II	LMS, UPS, other sarcoma, GIST, or osteosarcoma; advanced nonresectable/ metastatic disease	NCT02406781
Trabectedin, ipilimumab, & nivolumab	I, II	Locally advanced unresectable or metastatic STS	NCT03138161
Ipilimumab & nivolumab	II	Bone sarcoma or STS; measurable disease, and locally advanced/ unresectable or metastatic disease (at least 1 prior systemic therapy)	NCT02500797

Abbreviations: ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; GIST, gastrointestinal stromal tumor; IHC, immunohistochemistry; LMS, leiomyosarcoma; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; STS, soft-tissue sarcoma; uLMS, uterine leiomyosarcoma; UPS, undifferentiated pleomorphic sarcoma.

Neoadjuvant Chemotherapy in Soft Tissue Sarcomas

The use of neoadjuvant chemotherapy has been studied in a phase Ib/II trial for STS, which compared gemcitabine and docetaxel with gemcitabine and docetaxel with pazopanib [47]. This trial only accrued five patients (two LMS). Three patients discontinued because of toxicity, and the study closed. To our knowledge, there are no recommendations regarding neoadjuvant chemotherapy in uLMS.

Completed Clinical Trials with Unpublished Results

The Gynecologic Oncology Group phase III trial (GOG 277) was designed to compare gemcitabine and docetaxel plus doxorubicin with observation with and without an aromatase inhibitor in early-stage uLMS; however, it was closed early because of poor accrual. Therefore, observation after resection, according to the NCCN guidelines, can be considered in early-stage disease. Investigational agents that are being evaluated in STS include evofosfamide, a hypoxia-activated prodrug. Trials with evofosfamide alone or in combination with doxorubicin have been completed in STS, but the results are not yet available [48].

Ongoing Clinical Trials

There are multiple ongoing trials that include uLMS (Table 4). Table 4 is not an all-inclusive list, but it summarizes some of

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Table 5. Mutated genes in uLMS [103, 104]

Gene	Expression	Altered, %	Deletions, %	Mechanism
VIPR2	Downregulated	96	—	Smooth muscle proliferation
TP53	Downregulated	92	69	Apoptosis, genomic stability, and inhibition of angiogenesis
RB1	Downregulated	88	92	Inhibits cell cycle progression/deletion; associated with chromosomal instability
PTEN	Downregulated	75	81	Regulates PI3K/AKT/mTOR
YWHAE	Upregulated	83	—	Mediates signal transduction/cell division
MED12	Up- and downregulated	63	—	Represses or activates expression of other genes
miR-181b-5p	Upregulated	26	—	Associated with decreased expression of PI3K/AKT3/mTOR

Abbreviation: —, no data.

the ongoing research in the field. Immunotherapeutic agents, such as pembrolizumab (anti-programmed cell death protein 1 [PD-1]), nivolumab (anti-PD-1), and ipilimumab (anti-CTLA4), are being studied in STS. George et al. recently published a study in which 12 women received nivolumab alone. The median PFS was only 1.8 months (95% CI 0.8–not defined), and no objective responses were observed. Nivolumab as a single agent failed to demonstrate antitumor activity among uLMS patients without any biomarker selection. However, immunohistochemistry (IHC) expression of archival tumor material and analysis of changes in circulating immunophentypes are ongoing, and the study is being amended to evaluate treatment of metastatic disease [49].

Pembrolizumab, an anti-PD-1 agent, is also being evaluated alone (SARC028) and in combination with other agents: olaratumab, doxorubicin, axitinib, gemcitabine, tamlimogene laherparepvec, and cyclophosphamide. Tawbi et al. recently studied 80 patients, including 10 LMS patients, receiving pembrolizumab. No objective responses were observed in the STS cohort. PFS rates at 8 weeks were 50% in LMS. Longer clinical follow-up data are being evaluated to determine the therapeutic impact of single-agent pembrolizumab in STS and bone sarcoma and will be published along with immune monitoring in peripheral blood and tumor tissues [50]. Additionally, a phase II trial investigating nivolumab with and without ipilumumab was initiated in uLMS patients specifically, but has been suspended [51]. Nivolumab and ipilumumab are continuing to be evaluated together and in combination with trabectedin in STS. Whether the efficacy of immunotherapy in LMS is correlated with specific biomarkers such as PI3K pathway activation, loss of PTEN (both associated with anti-programmed death-ligand 1 [PD-L1] activity in melanoma), percentage of PD-L1 expression by IHC, amount of tumor-infiltrating lymphocytes, neoantigen load, or tumor mutational burden is currently being investigated [52–55].

Molecular Genetics and Potential Future Targets

As previously alluded to, specific targeting of tumors is likely the future of treatment. A recent study attempted to identify potential targets in uLMS by sequencing 84 samples across multiple centers. Although the authors identified reduced expression of established tumor suppressor genes such as *TP53*, *RB1*, and *PTEN*, they also identified VIPR2, a negative regulator of smooth muscle proliferation. VIPR2 was affected in 96% of samples and reduced in uLMS in comparison with normal myometrium. In addition, its deletion was a negative prognostic indicator in uLMS [53]. By identifying new potential oncogenes or tumor suppressor genes in individual tumors, we can potentially use established therapies or novel therapies to upregulate or downregulate specific genes. For example, imipramine, which is an FDA-approved antidepressant that upregulates VIPR2 expresssion, was proposed as an established therapy that could act by upregulating this tumor suppressor gene identified in uLMS [56]. The comprehensive and integrated genomic characterization of adult STS name many of the same tumor suppressor genes as above, but also make mention of miR-181b-5p, which is upregulated in LMS and associated with recurrence-free survival [57]. Interestingly, miR-181-b was thought to increase vascular smooth muscle proliferation and migration via the PI3K pathway [58]; however, this study found an association between increased expression of miR-181b-5p and low expression of PI3K pathway and targets mammalian target of rapamycin (mTOR) and AKT3 that are associated with phosphatase and tensin homolog (PTEN). Table 5 offers a summary of the major genes mutated in uLMS, how often they are affected, and whether they are up- or downregulated.

How Should Systemic Chemotherapy Be Sequenced?

Based on the data presented in this review, it is our opinion that frontline chemotherapy for uLMS should include either gemcitabine or doxorubicin. These agents should be administered alone if the patient cannot tolerate combination treatment, but ideally in combination with docetaxel (gemcitabine with docetaxel) or olaratumab (doxorubicin with olaratumab). According to all the clinical trials for uLMS, the most effective regimen in disease limited to the uterus has been the SAR005 regimen: gemcitabine (900 mg/m^2 day 1 and 8) plus docetaxel (75 mg/m^2 on day 8) every 21 days for four cycles, followed by doxorubicin (60 mg/m^2) every 21 days for four cycles. It is important to note that this regimen is not described in the NCCN guidelines and has not been studied in advanced disease.

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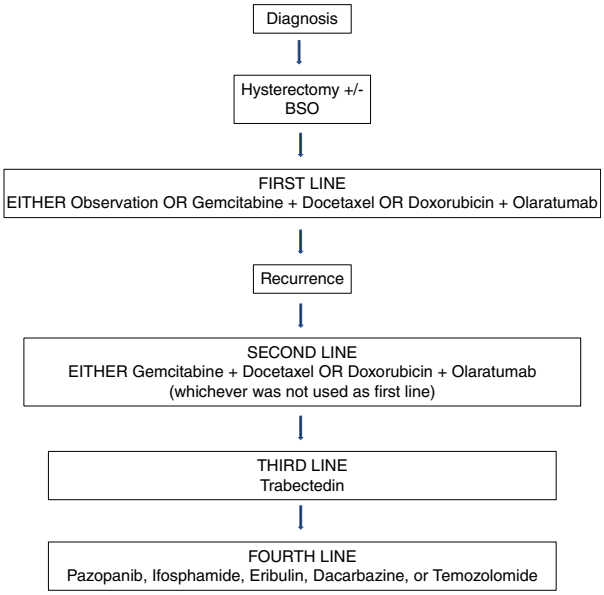

Figure 2. Suggested algorithm for chemotherapy treatment in uLMS.

Once patients with uLMS have recurred, patients should be encouraged to enroll in a clinical trial. If no trial is available and patients have not received prior doxorubicin, doxorubicin should serve as second-line systemic therapy. If doxorubicin was used previously without the use of gemcitabine and docetaxel, then gemcitabine and docetaxel should be used. If the patient already received gemcitabine and docetaxel, then doxorubicin could be administered with olaratumab. If the patient received gemcitabine and docetaxel followed by doxorubicin initially, trabectedin 1.5 mg/m^2 over a 24-hour infusion every 3 weeks would be an appropriate next line of therapy.

If not previously used, the third-line therapy for all uLMS patients should be trabectedin, as the phase II trial using this agent in advanced or recurrent disease had a 5.8-month PFS. If the patient already received trabectedin, another option for third-line or fourth-line therapy includes pazopanib. Other options could include ifosphamide, eribulin, or dacarbazine. Eribulin, although not FDA approved for uLMS, should be considered because it had comparable efficacy and fewer side effects than dacarbazine. See Figure 2 for suggested treatment algorithm.

Conclusion

uLMS is a devastating disease manifested by poor survival outcomes and short overall survival intervals once advanced or recurrent disease is diagnosed. Survival for stage I disease is poor in comparison with other uterine cancers [59, 60]. The cause is multifaceted—both tumor aggression and a lack of efficacious therapy in advanced or recurrent disease contribute to poor outcomes. Poor response to traditional chemotherapies has caused difficulty in establishing a consensus standard regimen among gynecological oncologists.

Starting in the 1980s, trials were commissioned to identify chemotherapeutics to treat sarcomas. Initially, single-agent doxorubicin was studied in three early GOG trials and no survival benefit was observed. Since that time, many agents have shown modest benefit; however, the NCCN has only supported ifosfamide, doxorubicin, and trabectedin as single-agent options for uLMS. Multiple trials have shown combination therapy to be efficacious in treating both previously resected and unresectable disease—most notably Hensley et al. and Maki et al. showed gemcitabine and docetaxel were both tolerable and active agents against STS [37, 38]. Both GOG87L and GOG131G confirmed that this regimen was active in patients with advanced, unresectable uLMS without prior chemotherapy and in patients with advanced, recurrent uLMS as a second-line treatement. SARC005 demonstrated improved response by adding four cycles of doxorubicin after the fixed-dose gemcitabine and docetaxel regimen, although the addition of bevacizumab showed no appreciable benefit [41].

Targeted therapy, specifically olaratumab, has shown promise in combination with doxorubicin versus doxorubicin alone. In addition, there are multiple ongoing trials that point to immunotherapy as a possible option to improve survival in uLMS. Tailoring immunotherapies to specific tumors in combination with traditional chemotherapies could provide great strides in an effort to more adequately treat uLMS. As targeted therapy and immunotherapy continue to evolve, it will be essential for providers to become more aware of the genetic and inflammatory profile of tumors. Ongoing clinical trials will hopefully offer new options to be used in combination with established agents. We continue to advocate for enrollment in these trials if available.

Additionally, researchers continue to explore other areas of evaluation and treatment of sarcomas, including surgical technique, staging methods, and response criteria [61]. This includes a proposal by Choi to embrace a new imaging-based response criteria specifically for sarcomas to better assess response [62].

The recommendations put forth in this review article are an attempt to establish the most current and effective treatment of recurrent and advanced uLMS. By forming a consensus for the efficacious treatment of this disease, a standard regimen will be established, which will be perpetually built upon and consequently result in increased survival. We realize that the ever-changing landscape of research in this arena will require consummate appraisal, and are excited by the multiple ongoing sarcoma trials. We look forward to further treatment development in the field, but until that time, the sequence of systemic chemotherapy proposed above has shown the most benefit in past trials.

Author Contributions

Conception/design: Rebecca C. Arend, Thomas J. Herzog
Collection and/or assembly of data: Rebecca C. Arend, Michael D. Toboni, Allison M. Montgomery
Data analysis and interpretation: Rebecca C. Arend, Michael D. Toboni, Allison M. Montgomery, Robert A. Burger, Alexander B. Olawaiye, Bradley J. Monk, Thomas J. Herzog
Manuscript writing: Rebecca C. Arend, Michael D. Toboni, Allison M. Montgomery, Robert A. Burger, Alexander B. Olawaiye, Bradley J. Monk, Thomas J. Herzog

Final approval of manuscript: Rebecca C. Arend, Robert A. Burger, Alexander B. Olawaiye, Bradley J. Monk, Thomas J. Herzog

Disclosures

Rebecca C. Arend: Clovis Oncology, AstraZeneca, VBL Therapeutics, Janseen, Tesaro, Puma (C/A); **Robert A. Burger:** Amgen, AstraZeneca, Clovis Oncology, Gradalis, Janssen, Merck, Morphotek, Tesaro, VBL Therapeutics (C/A); **Bradley J. Monk:** AstraZeneca, Tesaro, Inc. (C/A), Tesaro, Inc. (RF), AstraZeneca (H). The other authors indicated no financial relationships; **Thomas J. Herzog**: AstraZeneca, Caris, Clovis Oncology, Johnson & Johnson, Tesaro (SAB).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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